

Clomiphene Beats Metformin for PCOS Infertility

BY KATE JOHNSON
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NEW ORLEANS — Infertile women with polycystic ovary syndrome are three times more likely to become pregnant when treated with clomiphene citrate than they are when treated with metformin alone, according to a new study that is predicted to change clinical practice.

“Clomiphene remains the gold standard, and metformin, the newcomer, has been dethroned,” lead investigator Dr. Richard S. Legro said in an interview, adding that the results refuted his hypothesis that improving insulin sensitivity with metformin would have a more significant impact than clomiphene on fertility. “I will take the hit for being wrong in this hypothesis. ... Metformin was abysmal in terms of its cumulative pregnancy rate.”

The study was a prize paper candidate at the annual meeting of the American Society for Reproductive Medicine, where the results were called “stunning” by ses-



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DR. LEGRO

sion moderator Dr. Robert N. Taylor of Emory University, Atlanta. “This is the first time anyone has compared Clomid and metformin head to head,” commented Dr. William Buckett of McGill University, Montreal. “It will definitely change clinical practice because currently metformin is the drug of choice for treating this population,” he said in an interview.

The multicenter trial, conducted by the Reproductive Medicine Network and funded by the National Institutes of Health, included 626 infertile women with polycystic ovary syndrome (PCOS) who were randomized to either metformin extended release (2,000 mg/day), clomiphene citrate (50-150 mg/day for 5 days per cycle), or a combination of both, for six cycles.

The primary outcome was live birth, which was achieved in 22.5% of the clomiphene arm, compared with 7.2% of the metformin arm, a statistically significant difference. The live birth rate was even higher in the combined clomiphene/metformin arm (26.8%), compared with the clomiphene-only arm, but this difference was not statistically significant, said Dr. Legro of the Pennsylvania State University, Hershey.

“These findings are vitally important because people have been using metformin really like it’s vitamin M, thinking that it’s of benefit in infertile women with [PCOS]. But our results are relatively dismal for metformin, and certainly our first conclusion is you should not use metformin alone to achieve pregnancy.” Body mass index was a significant factor in pregnancy success, with obesity lowering the live birth rate. However, it did not alter the basic findings, although there was a nonsignificant

trend toward a benefit for combination therapy, compared with clomiphene alone, in obese women, he said.

The most remarkable finding of the study, according to Dr. Legro, was that fecundity, defined as live births per ovulated cycle, was significantly higher in clomiphene-treated subjects—at 9.6% in the combined arm and 10.2% in the clomiphene-only arm, compared with 5.1% in the metformin arm.

“This documents, really for the first

time, that all ovulations are not alike,” he said. “An ovulation with clomiphene is more fecund than an ovulation with metformin.” There was also a nonsignificant trend toward an increased rate of first-trimester pregnancy loss in the metformin group (40%), compared with the combined group (25.5%) and the clomiphene-only group (22.6%), said Dr. Legro.

“Although this study was not powered to detect differences in pregnancy loss rates, this certainly gives us caution about

the use of metformin to prevent pregnancy loss,” said Dr. Legro.

Dr. Legro noted that the study did not explore the effects of metformin for other indications in PCOS. “I do not want to condemn metformin overall—this study did not explore the effects of metformin on the prevention of diabetes or hirsutism—but I think we just have to be a little more cautious. If we’re using it alone, it’s probably a relatively ineffective agent for infertility.” ■

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Reference: 1. IMS Health, IMS MIDAS [12 months ending September 2005].

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